

ASTRAZENECA AB
 2002.10.22 2002-003122(+2002SE-000+50) (2003.08.21) C07D
 231/56, A61K 31/341, 31/4025, 31/416, 31/4427, C07D 403/04, 405/04,
 401/12, A61P 9/00, 25/00, 33/00

New indazole derivatives are c-Jun terminal kinase inhibitors used for treating e.g. Alzheimer's disease and cognitive disorders and Parkinson's disease (Eng)

C2003-189122 (NAE AG AL AM AT AU AZ BA BB BG BR BY BZ
 CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES
 FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG
 KP KR KZ LC LK LR LS LT LU LV MA MD MG MK
 MN MW MX MZ NO NZ OM PH PL PT RO RU SC
 SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ
 VC VN YU ZA ZM ZW) RAT BE BG CH CY CZ DE
 DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
 LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR
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Addnl. Data: MALMSTROEM J, SWAHN B
 2003.02.11 2003WO-SE00227, 2002.10.22 2002SE-003122.

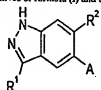
NOVELTY

Indazole derivatives (I) are new.

B(0-15), 14-C1, 14-C3, 14-C4, 14-C9, 14-D6, 14-G1B, 1
 14-H1, 14-J1A3, 14-J1A4, 14-N16) .7

DETAILED DESCRIPTION

Indazole derivatives of formula (I) and their salts are new.



(I)

R¹ = aryl or heteroaryl (both optionally substituted by at least one R², OR², OCOR², COOR², COR², CONR²R², NHCOR², NR²R², NHSO₂R², SO₂R², SO₂NR²R², SR², CN, halo or NO₂);
 R² = NO₂, NH₂, NR²R² or NR²R²;

R³, R⁴ = 1-6C alkyl, 2-6C alkenyl, 3-8C cycloalkyl-(0-6C)alkyl, 1-6C fluoroalkyl, heterocycle-(0-6C)alkyl or heteroaryl-(0-6C)alkyl (all optionally substituted by at least one B¹) or H, or

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R³ + R⁴ = 5-7 membered heterocyclyl containing 1-4 N, O or S heteroatoms (optionally substituted by at least one B¹);

B¹ = T, COR¹⁰ or oxo;

T = R¹⁰, COOR¹⁰, NHCOR¹⁰, NR¹⁰R¹⁰, CONR¹⁰R¹⁰, OR¹⁰, SO₂NR¹⁰R¹⁰, CN or halo;

R² = phenyl or heteroaryl (both optionally substituted by at least one T, OCOR¹⁰, NHSO₂R¹⁰, SO₂R¹⁰, SR¹⁰ or NO₂);

R³ = H, 1-6C alkyl, heterocycle-(0-6C)alkyl or hydroxy(1-6C)alkyl;

R⁴ = 1-6C alkyl, 3-8C cycloalkyl-(0-6C)alkyl, 5-8C cycloalkenyl-(0-6C)alkyl or R³-(1-6C)alkyl;

A = H, R⁴, OR⁴, OCOR⁴, COOR⁴, CONR⁴R⁴, NHCOR⁴, NR⁴R⁴, NHSO₂R⁴, SO₂R⁴, SO₂NR⁴R⁴, SR⁴, CN, halo, heterocycle-(0-6C)alkyl or heteroaryl-(0-6C)alkyl;

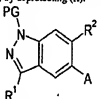
R⁵, R⁶ = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, heterocycle-(0-6C)alkyl or heteroaryl-(0-6C)alkyl (all optionally substituted by at least one B¹), or H, or

R⁷ + R⁸ = 5-7 membered heterocyclyl containing 1-4 N, O or S heteroatoms (optionally substituted by at least one B¹), and R⁹, R¹⁰ = H, 1-6C alkyl, 1-6C fluoroalkyl or hydroxy(1-6C)alkyl, or R⁹ + R¹⁰ = 5-7 membered heterocyclyl containing 1-4 N, O, or S heteroatoms (optionally substituted by at least one B¹), provided that (I) is not 6-amino-3-(4-fluorophenyl)-indazole, 6-amino-

3-phenyl-indazole, 6-nitro-3-phenyl-indazole and 6-nitro-3-(4-nitrophenyl)-indazole, and has no quinazoline in the R³ position.

INDEPENDENT CLAIMS are also included for:

(1) new intermediate compounds of formula (II), and
 (2) preparation of (I) by deprotecting (II).



(II).

PG = amino protecting group.

ACTIVITY

Neuroprotective; Nootropic; Antiparkinsonian; Anticonvulsant; Anti-HIV; Cytostatic; Antiinflammatory; Antipyretic; Analgesic.

MECHANISM OF ACTION

c-Jun N-terminal kinase (JNK) inhibitor.

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In a scintillation proximity assay (SPA) based on the inhibition of JNK3 catalyzed transfer of the γ-phosphate group of [γ-³²P] adenosine triphosphate (ATP) to biotinylated activating transcription factor (ATF)-2, (I) exhibited K_i values of 0.001-10000 (especially 0.001-300) nM.

USE

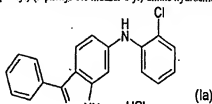
Used central or peripheral neurological degenerative disorders including Alzheimer's disease, cognitive disorders, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia Parkinson's type, Parkinson dementia complex of Gaum, HIV dementia, corticobasal degeneration, dementia pugilistica, Down's syndrome, postencephalic parkinsonism, progressive supranuclear palsy, Pick's disease, Niemann-Pick's disease, epilepsy, peripheral neuropathy, spinal cord injury, head trauma, cancer, edema, analgesia, fever and pain (e.g. neuromuscular pain, headache, cancer pain, dental pain and arthritis pain) (all claimed).

ADVANTAGE

(I) Are potent inhibitors of JNK, which inhibit the expression of inducible proinflammatory proteins.

SPECIFIC COMPOUNDS

64 Compounds (I) are specifically claimed e.g. (2-chlorophenyl)-(3-phenyl-1H-indazol-6-yl)-amine hydrochloride (Ia).



(Ia)

ADMINISTRATION

The dosage is 0.01-250 mg/kg/day perorally or 0.001-250 mg/kg/day parenterally.

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EXAMPLE

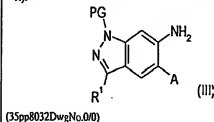
Palladium acetate (15.1 mg) and (S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ((S)-BINAP) (61.2 mg) were mixed in dry tetrahydrofuran (3 ml) for 5 minutes under a nitrogen atmosphere. 1-Bromo-2-chlorobenzene (75 μ l) and 6-amino-3-phenyl-indazole-1-carboxylic acid tert-butyl ester (199.8 mg) were added, followed by cesium carbonate (295.5 mg). The reaction was stirred at 60°C for 7 hours under a nitrogen atmosphere. Then, additional palladium acetate (15 mg), ((S)-BINAP) (61.4 mg) and 1-bromo-2-chlorobenzene (75 μ l) were added. The reaction mixture was stirred at 60°C for 18 hours, followed by work-up to give 6-(2-chloro-phenylamino)-3-phenyl-indazole-1-carboxylic acid tert-butyl ester.

To a solution of this compound (144.3 mg) in methanol (2 ml) was added 4M HCl in diethylether (1 ml). The reaction mixture was stirred at ambient temperature for 24 hours. The solvent was evaporated and work up produced (2-chlorophenyl)-(3-phenyl-1H-indazol-6-yl)-amine hydrochloride (1a) (117.1 mg; 87%).

TECHNOLOGY FOCUS

Organic Chemistry - Preparation (claimed): Preparation of (I) comprises e.g. reacting an amine compound of formula (II) with R^5-X

and deprotecting (II: $R^4 = NR^5R^6$; $R^5 = H$) to give (I: $R^2 = NR^3R^6$, $R^6 = H$).



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